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09/358,141	07/20/1999	JEFFREY R. SAMPSON	10990393-1	1170

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AGILENT TECHNOLOGIES, INC.
INTELLECTUAL PROPERTY ADMINISTRATION, LEGAL DEPT.
P.O. BOX 7599
M/S DL429
LOVELAND, CO 80537-0599

EXAMINER

SCHMIDT, MARY M

ART UNIT PAPER NUMBER

1635

DATE MAILED: 01/02/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/358,141

Applicant(s)

SAMPSON, JEFFREY R.

Examiner

Mary M. Schmidt

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 17 October 2002.

2a) ☐ This action is FINAL.

2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-8 and 10-24 is/are pending in the application.

4a) Of the above claim(s) 10-18 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☐ Claim(s) 1-8 and 19-24 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on 20 July 1999 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 20.

4) ☐ Interview Summary (PTO-413) Paper No(s) _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other:

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DETAILED ACTION

1. Applicant's election with traverse of T7 RNA Polymerase in the response filed 10/17/02 is acknowledged. The traversal is on the ground(s) that "those of ordinary skill in the art can readily test various combinations of nucleotides and/or analogs with various polymerases to define other sets that can appropriately be used in accordance with the present invention.... A search limited by RNA polymerase would identify too many references because it would identify any reference using that polymerase with any nucleotide or nucleotide analog. The search would simultaneously identify too few references because it would not identify references that might utilize relevant sets of nucleotides with other polymerases. Applicant respectfully submits that a single search for nucleotides that preferentially form intermolecular base pairs would appropriately define the literature relevant to the present invention, regardless of the particular polymerase being employed in a given reaction." Applicants further submit that the strategy taught by the supplied Nguyen and Southern reference was not limited to any particular polymerase. This is not found persuasive because for the consideration of both prior art and 35 U.S.C. 112, first paragraph, issues regarding the instant claims, one of skill in the art would necessarily consider what analogues would be able to be used for the instantly claimed methods. The Nguyen and Southern paper taught on page 3905 that "For practical applications it will be necessary to incorporate the modified bases in the nucleic acid fragments to be analyzed by an enzymatic reaction, constraining the choice of modified nucleosides to those whose 5'-triphosphates can be used as substrates for DNA polymerases. From the large number of

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modified nucleosides described in the literature we chose d4EtC to replace natural deoxycytidine (dC)...." Therefore, they do narrow there experimental conditions to what is practical, use of known modified nucleosides, which are useful with DNA polymerases. Therefore, while they do suggest use of this technique in both DNA and RNA studies of secondary structure, they specifically state that one skilled in the art uses those modified nucleosides known to be useful with certain class of polymerase.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 10-18 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement mailed 1/30/01 in the response filed 3/2/01. Here applicant elected Group IA, claims 1-9 designating RNA polymerases. (Note that claim 10 was inadvertently included in Office action mailed 5/23/01 and is not included in the present Office action since it belonged to a non-elected group.) The traversal was addressed, and the restriction maintained in the Office action mailed 5/23/01.

Drawings

3. The drawings have been reviewed. A copy of the PTO 948 is attached. Correction is required.

Claim Objections

4. Claim 20 is objected to because of the following informalities: line 2 states the following typographical error: "providing a at least one...". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-8 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to methods of synthesizing an unstructured nucleic acid comprising the steps of providing a nucleic acid template strand including a first template sequence element and a second template sequence element that is substantially complementary to the first template sequence element, providing a collection of nucleotide precursors sufficient to synthesize a nucleic acid strand complementary to at least a portion of the template nucleic acid strand, which portion includes the first and second template sequence elements, the collection including the first and second complementary nucleotides, wherein the first and second complementary nucleotides have a reduced ability to form an intramolecular base pair but can form an

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intermolecular base pair; and contacting the template and the nucleotides with an RNA polymerase enzyme characterized by an ability to polymerize the nucleotides under conditions and for a time sufficient for incorporation of the nucleotides to synthesize the unstructured nucleic acid so that said first complementary sequence element and said secondary complementary sequence element of the unstructured nucleic acid do not interact with one another.

Dependent claim 2 states that the step of providing nucleotides comprises the step of providing at least one nucleotide having a purine analog and at least one nucleotide having a pyrimidine analog such that said purine analog and said pyrimidine analog are not capable of forming a stable hydrogen bonded base pair.

Dependent claims 3-8 state certain deoxynucleotides for addition in the step of providing nucleotides.

Dependent claims 19-24 state certain ribonucleotides for addition in the step of providing nucleotides.

The specification as filed teaches by way of example use of a DNA Polymerase (Bst) for incorporation of D and S modified nucleotides. The specification as filed teaches only prophetically the use of any such modified bases for incorporation by T7 RNA Polymerase.

MPEP 608.01(p) states that "“Essential material” is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention,

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or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference....”

In the instant invention, the claims are drawn to a broad scope of methods of synthesizing any type of unstructured nucleic acid molecule by providing any type of nucleic acid template (DNA, RNA, etc.), providing any type of nucleotide precursors (DNA, RNA, etc.) for synthesis of the unstructured nucleic acid with the elected T7 RNA polymerase. As taught in the IDS reference 12 from IDS filed 1/8/01 (Milligan and Uhlenbeck, “Synthesis of Small RNAs Using T7 RNA Polymerase, 1989) the use of T7 RNA polymerase to synthesize RNA was accepted. However, as taught by Irtolova-Donnelly et al. more recently (*Biochemistry*, 1998, Vol. 37, pp. 12933-12942), T7 RNA polymerase is not useful for the incorporation of some modified nucleobases into ribozyme RNAs. Irtolova-Donnelly et al. state on page 12936, col. 2, line 3, that “[i]nitial efforts to incorporate m2GalphaS were unsuccessful using T7 RNA polymerase, probably because the methyl group occupies a prominent position in the minor groove that is likely to be involved in the error-reading mechanism of the polymerase.... No incorporation was observed even at high ratios of m2GTPalphaS to GTP (data not shown).” Thus, one of skill in the art would not have accepted that any known nucleotide analogue would have been acceptable for use in the claimed methods steps since the genus of all such possible nucleotide analogs does not provide one skilled in the art with a representative number of species of such analogues known to function specifically with T7 RNA polymerase. Since the specific precursors used are an essential feature of the claimed invention, such information may not be incorporated by

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reference. The teachings in the specification as filed drawn to specific precursors specific for Bst DNA polymerase do not specifically correlate to a description of precursors that function with T7 RNA polymerase. One of skill in the art would not have recognized that applicant was in possession of a representative number of species of specific nucleotide precursors for making the breath of claimed UNAs with T7 RNA polymerase.

Response to Arguments

Since the previous Office action mailed 5/23/01 asserted, based on the teachings of U.S. Patent 6,184,364) that T7 RNA polymerase would not be able to incorporate deoxy precursors, applicant responded that Padilla, Sousa et al., and Sousa taught that "nucleotides other than ribonucleotides, could be incorporated into a nucleic acid template by an RNA polymerase at the time of the invention." The T7 RNA polymerases taught by the cited references are the Y639F point mutant of T7 RNA polymerase. Ortoleva-Donnelly et al. further taught on page 12936, col. 2, line 9, that "[w]e had previously obtained and overexpressed a Y639F point mutant of T7 RNA polymerase to perform NAIM with 2'-deoxynucleotides. This mutation was reported to cause reduced selectivity for the 2'-position of the nucleotide during transcription.... The mutant polymerase efficiently incorporates 2'-deoxy, 2'-methoxy, 2'-fluoro, and 2'-thio nucleotide triphosphates into RNA transcripts.... " Therefore, the prior art did in fact disclose one T7 RNA polymerase point mutant that was able to incorporate deoxynucleotide precursors. However, as argued above, the specific polymerase and precursor combinations are considered essential

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material for the instant invention since the invention is not adequately described without them. Since the specification as filed does not disclose the specific use of the Y639F T7 RNA polymerase mutant for use in the claimed methods, the specification as filed still does not support a written description of a representative number of species of deoxynucleotide-precursors for use in making unstructured nucleic acids via T7 RNA polymerase.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Inquiries relating to the status of this application may also be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.



M. M. Schmidt

December 28, 2002